Ref. (11) + (12)

1+2

PATRO INFORMATION K.K.
Translation, Search and Information Service

Toranomon 37 Mori Bldg.
3-5-1 Toranomon
Minato-ku
Tokyo 105
Japan

FACSIMILE:+81-3-5470-1931
TELEPHONE:+81-3-5470-1930
Internet-MAIL: abe00736@niftyserve.or.jp
http://www.iijnet.or.jp/PATRO

November 13, 1996

Dr. Manuel Kunst
European Patent Attorney
Dr. Volker Buss
Head of Patents Infection/Tumor
Patent Department
Ciba-Geigy AG
CH-4002 Basle
SWITZERLAND

CONFIRMATION COPY

VIA FACSIMILE
TOTAL 20 SHEETS

Re: Translation of Parts of JP 3-106675 and 3-106673
Your Ref.: FD 4.4/KU, Our Ref.: 962511-CIBA

Dear Sirs,

This follows our facsimile of October 31, 1996, regarding the above identified matter.

Please find attached partial translations of Kokai (Jpn. Unexamined Patent Publication) Nos. 3-106875 and 3-106873.

If you need any further assistance, please so inform us.

Very truly yours,
PATRO INFORMATION

H. Sato
Director

CH/sy
Attach: JPP'875 & JPP'873 Partial Trans.
Mail: Debit note

¥ 730'600,-

Kokai (Japanese Unexamined Patent Publication) No.3-106875
Title of the Invention: 1-(3-Pyridylmethyl)phthalazine Derivatives
Publication Date: May 7, 1991
Patent Application No. 1-246074
Filing Date: September 20, 1989
Applicant: MORISHITA PHARM KK

— — — — — — — — — — — — — — —

When the compounds (I) of the present invention are used as a pharmaceutical drug, they can be administered both orally and parenterally. The dose of the compounds (I), which may vary according to the patient's age, weight, or severity of the disease, is usually in the range of 5 to 2000 mg per day, and preferably 10 to 500 mg per day.

In addition, the compounds (1) of the present invention may be used in a mixture with excipients suitable for oral or parenteral administration. Examples of such ecxipients include, for example, lactose, sucrose, kaolin, crystalline cellulose, corn starch, magnesium stearate, glucose, talc, sodium chloride, lecithin, gelatin, peptin, vegetable oils, and the like. It can take a form of solid preparations such as tablets, particles, powders, capsules, pills and the like, and may include adjuvants such as stabilizers, wetting agents, emulsifying agents, and the like. They can also be used in the form of injections for parenteral adiministration.

The invention will be understood more readily with reference to the following examples.

Example 1

Compound (II) (1.0 g) and m-chloroaniline (2.5 g) were heated under stirring at 100 °C for 3 hours. The reaction mixture was purified by a silica gel column chromatography (the developing solvent, methylen chloride : methanol 50:1) and was recrystallized from a mixture of ethanol-isopropyl ether to give

1-(3-chloroanilino)-4-(3-pyridylmethyl)phthalazine (0.3 g).

m.p.: 208 to 209 °C.

IR νmax (Nujol) cm^{-1}: 3250 (NH).

Mass m/z : 346 (M^+).

^1H-NMR (DMSO-d_6) δ(ppm):

4.62 (2H, s, $-CH_2-$),
7.08-7.09 (1H, d, J=8.0 Hz, benzene-H),
7.31-7.41 (2H, m, benzene-H, pyridine-H),
7.68-7.72 (1H, d, J=8.0 Hz, benzene-H),
7.85-7.89 (1H, d, J=8.0 Hz, benzene-H),
7.96-8.02 (2H, m, phthalazine-H),
8.21-8.27 (2H, m, phthalazine-H, benzene-H),
8.40-8.57 (1H, d, J=6.0 Hz, pyridine-H),
8.62-8.65 (2H, m, phthalazine-H, pyridine-H),
9.33 (1H, s, NH)

Elemental analysis ($C_{20}H_{15}N_4Cl$)

Calculated (%): C, 69.26; H, 4.35; N, 16.15.

Found (%): C, 69.09; H, 4.42; N, 16.00.

Example 2

Compound (II) (2.0 g) and 2,5-dimethoxyaniline were heated to reflux in ethanol for 4 hours. After evaporation of the solvent under reduced pressure, the residue was dissolved in methylene chloride, washed with water, and dried on Na_2SO_4. The residue obtained after evaporation of the solvent was purified by a silica gel column chromatography (the developing solvent, methylene chloride:methanol 50:1) and recrystallized from ethanol to give
1-(2,5-dimethoxyanilino)-4-(3-pyridylmethyl)phthalazine (1.0 g).

m.p.: 163 to 166 °C.

IR νmax (Nujol) cm^{-1}: 3475 (NH).

Mass m/z : 372 (M^+).

^1H-NMR (DMSO-d_6) δ(ppm):

3.75 (3H, s, $-OCH_3$),

3.82 (3H, s, $-OCH_3$),

4.59 (2H, s, $-CH_2-$),

6.66-6.70 (1H, d, J=9.0 Hz, benzene-H),

7.00-7.04 (1H, d, J=9.0 Hz, benzene-H),

7.26-7.31 (1H, t, J=6.0 Hz, pyridine-H),

7.66-7.69 (1H, d, J=7.0 Hz, pyridine-H),

7.86-7.96 (3H, m, phthalazine-H, benzene-H),

8.17-8.20 (1H, d, J=8.0 Hz, phthalazine-H),

8.37-8.46 (3H, m, NH, benzene-H, pyridine-H),

8.63 (1H, s, pyridine-H).

Elemental analysis ($C_{22}H_{28}N_4O_2$)

Calculated (%): C, 70.95; H, 5.41; N, 15.04.

Found (%): C, 70.66; H, 5.57; N, 14.96.

Examples 3

Compound (II) (2.0 g) and piperidine (2.0 g) were heated to reflux at 100 °C for 2 hours. The reaction mixture was dissolved in methylene chloride, washed with water, and dried on Na_2SO_4. The residue obtained after evaporation of the solvent was recrystallized from ethanol to give 1-piperidino-4-(3-pyridylmethyl)phthalazine (1.0 g).

m.p.: 136 to 137 °C.

Mass m/z : 304 (M^+).

^1H-NMR (DMSO-d_6) δ(ppm):

1.65-1.78 (6H, br, piperidine-H),

3.31-3.37 (4H, br, piperidine-H),

4.62 (2H, s, $-CH_2-$),

7.27-7.32 (1H, dd, J=8.0, 5.0 Hz, pyridine-H),

7.67-7.70 (1H, d, J=8.0 Hz, pyridine-H),

7.90-7.94 (2H, m, phthalazine-H),

8.05-8.09 (1H, m, phthalazine-H),

8.22-8.25 (1H, m, phthalazine-H),

8.40-8.42 (1H, d, NH, J=5.0 Hz, pyridine-H),

8.63-8.66 (1H, s, pyridine-H).

Elemental analysis ($C_{19}H_{20}N_4$)

Calculated (%): C, 74.97; H, 6.62; N, 18.40.

Found (%): C, 74.77; H, 6.80; N, 18.32.

Example 4

Compound (II) (2.0 g), N-(2,5-dimethoxyphenyl)piperadine (2.0 g), and triethylamine (1.0 g) in DMF were heated under stirring at 100 °C for 5 hours. The reaction mixture was dissolved in methylene chloride, washed with water, and dried on Na_2SO_4. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography (the developing solvent, methylene chloride:methanol 50:1) and recrystallized from methanol-isopropyl ether to give 1-[N-(2,5-dimethoxyphenyl)piperadino]-4-(3-pyridylmethyl)phthalazine (1.9 g).

m.p.: 122 to 125 °C.

Mass m/z : 441 (M^+).

^{1}H-NMR (DMSO-d_6) δ(ppm):

3.18-3.32 (4H, br, piperadine-CH_2-),

3.45-3.60 (4H, br, piperadine-CH_2-),

3.71 (3H, s, -OCH_3),

3.76 (3H, s, -OCH_3),

4.64 (2H, s, -CH_2-),

6.50-6.57 (2H, m, benzene-H),

6.87-6.90 (1H, d, J=9.0 Hz, benzene-H),

7.28-7.33 (1H, m, pyridine-H),

7.68-7.71 (1H, d, J=8.0 Hz, pyridine-H),

7.93-7.96 (2H, m, phthalazine-H),

8.16-8.20 (1H, m, phthalazine-H),

8.25-8.29 (1H, m, phthalazine-H),

8.40-8.43 (1H, dd, J=5.0, 1.5 Hz, pyridine-H),

8.63-8.64 (1H, d, J=1.8 Hz, pyridine-H).

Elemental analysis ($C_{26}H_{27}N_5O_2$)

Calculated (%): C, 70.72; H, 6.16; N, 15.86.
Found (%): C, 70.54; H, 6.49; N, 15.69.

Example 5 to 15

The compounds of examples 5 to 15 were synthesized in a similar manner to either of the methods described in examples 1, 2, 3 and 4. The structural formulae and melting points of the compounds obtained are summarized in Table 1.

Table 1

No.	R^1	R^2	m.p. (°C)
5	phenyl-	H	174-176
6	2-fluorophenyl-	H	146-148
7	3-fluorophenyl-	H	191-193
8	4-fluorophenyl-	H	220-222
9	4-chlorophenyl-	H	196-197
10	4-hydroxyphenyl-	H	249-252
11	isobutyl-	H	143-146 188 (2HCl)+1
12	isoamyl-	H	155-160 (2HCl)
13	neopentyl-	H	136-138
14	metyl	$-CH_3$	230 (2HCl)+1
15	imidazol-1-yl-		146-148

Note:
+1 (2HCl) signifies 2 hydrochloride.

17

+2 m.p. sinifies a decomposition point.

— — — — — — — — — — — — — —

Examples of pharmaceutical preparations

Preparation example 1

Active ingredient	50 mg
Lactose	200 mg
Crystalline cellulose	40 mg
Magnesium stearate	5 mg

The above compounds were admixed according to the conventional method and compressed into tablets containing 50 mg of the main drug.

Preparation example 2

Active ingredient	50 mg
Lactose	90 mg
Corn starch	60 mg
Talc	30 mg
Magnesium stearate	10 mg

The above compounds were granulated according to the conventional method to make granules.

Preparation example 3

Active ingredient	10 mg
Solubilizer (used as desired)	a suitable amount
Sodium chloride (used as desired)	a suitable amount
Distilled water for injection	1 ml

The above compounds were admixed according to the conventional method and then filled into ampoules to make ampoules for injection.

Pharmacological study

(1) Platelet aggregation inhibitory action in vitro

Platelet aggregation inhibitory action of the compounds of the present invention was measured according to the method

described by Born (G.V. Born, Nature, 927-929, (1962)). Thus, citric acid-added blood was drawn from Japanese white male rabbits, which was then centrifuged to obtain platelet-rich plasma (PRP) and platelet-poor plasma (PPP). 1.5 µl of the test compounds dissolved in dimethyl sulfoxide (DMSO) was added to 270 µl of PRP. After incubating at 37 °C for 1 minute, arachidonic acid (AA) was added to induce aggregation. Platelet aggregation was measured by NKK Hematracer, and 50% inhitibory concentrations (IC_{50}, µM) of the test compounds were obtained from the concentration-inhibition ratio curve. Aspirin was used as a control drug. The results of the representative examples are shown in Table 2.

Table 2

Test cmpds. Example No.	Arachidonic acid IC50 µM	Test cmpds. Example No.	Arachidonic acid IC50 µM
1	10.0	10	8.5
3	9.1	11	20.9
5	10.0	13	12.0
6	20.1	15	9.0
7	6.5		
8	14.4	Aspirin	172

(2) Effects on an arachidonic acid (AA)-induced pulmonary thrombosis death model

This study was performed according to the method described by Silver et al. (Science, 183, 1085 (1974)). Thus, Japanese white male rabbits after 24-hour fasting were administered AA (1.6 mg/kg) dissolved in 0.1 M sodium carbonate in the veins of the ear to induce pulmonary thrombosis death due to platelet aggregation. The test compounds at a dose of 10 mg/kg were intravenously injected one hour before AA administration. The

effects were assessed by the death rate at 2 hour after AA administration. The results are shown in Table 3.

Table 3

Example No.	No. of death/Total number
11	1/4
Control group	3/3

Effects of the invention

The compounds of the present invention have shown excellent activities more potent than aspirin in in vitro platelet aggregation inhibition tests, and thus they are useful as anti-thrombotic agents.

Kokai (Japanese Unexamined Patent Publication) No.3(1991)-106873
Title of the Invention: 1-Pyridyl Phthalazine Derivatives and Platelet Aggregation Inhibitors Containing the Same
Publication Date: May 7, 1991
Patent Application No. 1-246073
Filing Date: September 20, 1989
Applicant: MORISHITA PHARM KK

Platelet aggregation inhibitors according to the present invention contain compounds of said general formula (I) as an active principle.

When the compounds (I) of the present invention are used as a pharmaceutical drug, they can be administered both orally and parenterally. The dose of the compounds (I), which may vary according to the patient's age, weight, or severity of the disease, is usually in the range of 5 to 2000 mg per day, and preferably 100 to 500 mg per day.

In addition, the compounds (I) of the present invention may be used in a mixture with excipients suitable for oral or parenteral administration. Examples of such excipients include, for example, lactose, sucrose, kaolin, crystalline cellulose, corn starch, magnesium stearate, glucose, talc, sodium chloride, lecithin, gelatin, peptin, vegetable oils, and the like. It can take a form of solid preparations such as tablets, particles, powders, capsules, pills and the like, and may include adjuvants such as stabilizers, wetting agents, emulsifying agents, and the like. They can also be used in the form of injections for parenteral administration.

The invention will be understood more readily with reference to the following examples.

Example 1

1-chloro-4-(3-pyridyl)phthalazine (20.0 g) and aniline (23.0 g) were heated under stirring at 100 °C for 30 minutes. The solidified reaction mixture was dissolved in methylene chloride and washed sequentially with a dilute aqueous solution of sodium carbonate and water. The organic phase was dried on Na_2SO_4, evaporated, and then the residue was recrystallized from ethanol to give 1-anilino-4-(3-pyridyl)phthalazine (19.3 g).
m.p.: 204 to 206 °C.
IR νmax (Nujol) cm^{-1}: 3360 (NH).
Mass m/z : 298 (M^+).
^1H-NMR (DMSO-d_6) δ(ppm):

7.08 (H, t, J=7.3 Hz, aniline-H),
7.39 (H, t, J=7.9 Hz, aniline-H),
7.59-7.64 (1H, dd, J=7.8, 4.8 Hz, pyridine-H),
7.86-8.14 (6H, m),
8.69-8.77 (2H, m),
8.88-8.89 (1H, d, J=1.9 Hz, pyridine-H),
9.35 (1H, s, NH).

Elemental analysis ($C_{19}H_{14}N_4$)
Calculated (%): C, 76.49; H, 4.73; N, 18.77.
Found (%): C, 76.20; H, 4.74; N, 19.05.

Example 2

1-chloro-4-(3-pyridyl)phthalazine (3.0 g) and 2,2-dimethylpropyl amine (4.2 g) were heated under stirring at 100 °C for 3.5 hours. The amine was evaporated under reduced pressure and the residue was dissolved in methylene chloride. The organic phase was washed sequentially with water, a dilute aqueous solution of sodium hydroxide and water, and then was dried on Na_2SO_4. The solid obtained after evaporation of the solvent was recrystallized from a mixture of ethanol and isopropyl ether to give
1-(2,2-dimethylpropylamino)-4-(3-pyridyl)phthalazine (1.4 g).
m.p.: 225 to 227 °C.

IR vmax (Nujol) cm^{-1}: 3260 (NH).

Mass m/z : 292 (M^+).

^{1}H-NMR (DMSO-d_6) δ(ppm):

1.01 (9H, s, CH_3 x 3),

3.60 (2H, d, J=6.0 Hz, $\underline{CH_2}C(CH_3)_2$),

7.40 (1H, t, J=6.0 Hz, NH),

7.55-7.65 (1H, m, pyridine-H),

7.75-8.10 (4H, m)

8.50 (1H, d, J=8.0 Hz, benzene-H),

8.75 (1H, d, J=7.5 Hz, pyridine-H),

8.82 (1H, d, J=2 Hz, pyridine-H).

Elemental analysis $C_{18}H_{26}N_4$

Calculated (%): C, 73.94; H, 6.90; N, 19.16.

Found (%): C, 74.16; H, 4.16; N, 19.11.

Examples 3 to 22

In accordance with the method of example 1 or 2, the compounds of examples 3 to 22 were synthesized. The structural formulae and the melting points of the compounds obtained are summarized in Table 1.

Table 1

No.	Py	R^1	R^2	R^3	Melting Point
3	3	H	3-Cl-Ph-[1)]	H	226-227
4	3	H	2-F-Ph-	H	124-126
5	3	H	3-F-Ph-	H	212-213
6	3	H	4-F-Ph-	H	207-210
7	3	H	24-F-Ph-[2)]	H	190-191
8	3	H	4-CN-Ph-	H	251-253
9	3	H	n-butyl-	H	148-150
10	3	H	iso-butyl-	H	135-137
11	3	H	sec-butyl-	H	165-168
12	3	H	1-Et-Pr-[3)]	H	220-203
13	3	H	n-heptyl-	H	175-176 (2HCl salt)
14	3	H	3-Mo-Pr-[4)]	H	189-194 (2HCl salt)
15	2	H	Ph-	H	183-185
16	2	H	neopentyl-	H	175-177
17	4	H	Ph-	H	225-228
18	4	H	neopentyl-	H	216-218
19	3	H	imidazol-1-yl-		182-183
20	3	H	diMeo-Ph-Pi-[5)]		158-159
21	3	OCH_3	3-Cl-Ph-	H	234-235
22	3	OCH_3	imidazol-1-yl-		176-177

Note: The number in the Py column indicates the position where pyridine is bound.

1) Ph- signifies phenyl radical and 4-Cl-Ph- signifies 4-chlorophenyl radical.

2) 24-F-Ph- signifies 2,4-difluorophenyl radical.

3) 1-Et-Pr- signifies 1-ethylpropyl radical.

4) 3-Mo-Pr- signifies 3-morpholinopropyl radical.

5) diMeo-Ph-Pi- signifies N-(2,5-dimethoxyphenyl)piperadinyl radical.

Example 23

1-chloro-4-(2-pyridyl)phthalazine (5.6 g) and n-butyl mercaptane (2.2 g) in 150 ml of ethanol were heated to reflux in the presence of 3.5 g of K_2CO_3 for 18 hours. After the solvent was evaporated under reduced pressure, the residue was dissolved in methylene chloride, washed with water, and dried on Na_2SO_4. The residue obtained after evaporation of the solvent was recrystallized from isopropyl ether to give 1-butylthio-4-(2-pyridyl)phthalazine (3.0 g).

m.p.: 63 to 64 °C.

Mass m/z : 295 (M^+).

^{1}H-NMR (DMSO-d_6) δ(ppm):

0.95 (3H, t, J=7.3 Hz, CH_3),

1.43-1.58 (2H, m, $C\underline{H_2}CH_3$),

1.74-1.86 (2H, m, $C\underline{H_2}CH_2CH_3$),

3.49 (2H, t, J=7.3 Hz, $SC\underline{H_2}C3$),

7.61-7.64 (1H, m, benzene-H),

8.01-8.20 (5H, m)

8.60-8.64 (1H, m, pyridine-H),

8.81-8.84 (1H, m, pyridine-H).

Elemental analysis $C_{17}H_{17}N_2S$

Calculated (%): C, 69.11; H, 5.80; N, 14.22.

Found (%): C, 69.06; H, 5.74; N, 14.24.

Examples 24

In accordance with the method of example 23, 1-(4-chlorophenoxy)-4-(3-pyridyl)phthalazine (m.p. 166 to 168 °C) was obtained.

Example 25

After 1.4 g of sodium hydroxide was dissolved in 80 ml of ethanol, 2.8 g of 2-mercapto-4-methylpyrimidine hydrochloride was added. The mixture was stirred at room temperature for some time and then 4.0 g of 1-chloro-4-(3-pyridyl)phthalazine was added. The mixture was heated to reflux for 3.5 hours. The reaction mixture was concentrated to dryness, and the residue was dissolved in methylene chloride, washed with water, and dried. After evaporation of the solvent, the residue was recrystallized from ethanol to give 1-(4-methylpyrimidine-2-ylthio)-4-(3-pyridyl)phthalazine (4.0 g).

m.p.: 175 to 177 °C.

Mass m/z : 331 (M^+).

^{1}H-NMR (DMSO-d_6) δ(ppm):

2.37 (3H, s, CH_3),

7.17-7.19 (1H, d, J=5.1 Hz, pyridine-H),

7.67-7.73 (1H, td, J=4.9, 0.7 Hz, pyridine-H),

8.08-8.09 (3H, m, pyridine-H, phthalazine-H),

8.25-8.36 (3H, m, pyridine-H, phthalazine-H),

8.84-8.86 (1H, dd, J=1.6, 4.9 Hz, pyridine-H),

9.01 (1H, d, J=0.7 Hz, pyridine-H).

Elemental analysis $C_{18}H_{13}N_5S$

Calculated (%): C, 65.23; H, 3.95; N, 21.13.

Found (%): C, 64.96; H, 3.84; N, 21.00.

Example 26

Sodium hydroxide (2.4 g) was added to 100 ml of ethanol. After the sodium hydroxide dissolved, 1-chloro-4-(2-pyridyl)phthalazine (6.0 g) was added and heated to reflux for 3 hours. After evporation of the solvent, the residue was

dissolved in methylene chloride, washed with water, and dried. After evporation of the solvent under reduced pressure, the residue obtained was recrystallized from ethanol to give 1-ethoxy-4-(2-pyridyl)phthalazine (2.4 g).

m.p.: 129 °C.

Mass m/z : 251 (M^+).

^{1}H-NMR (DMSO-d_6) δ(ppm):

1.53 (3H, t, J=7.0 Hz, CH_3),

4.73 (2H, q, J=7.0 Hz, CH_3),

7.56-7.62 (1H, m, phthalazine-H),

7.98-8.07 (4H, m, pyridine-H, phthalazine-H),

8.26-8.29 (3H, m, pyridine-H),

8.57-8.61 (1H, m, pyridine-H),

8.79-8.81 (1H, m, pyridine-H).

Elemental analysis $C_{15}H_{13}N_3S$

Calculated (%): C, 70.56; H, 5.13; N, 16.46.

Found (%): C, 70.88; H, 5.37; N, 16.76.

— — — — — — — — — — — — — —

Examples of pharmaceutical preparations as a platelet aggregation inhititor

Preparation example 1

Active ingredient	50 mg
Lactose	200 mg
Crystalline cellulose	40 mg
Magnesium stearate	5 mg

The above compounds were admixed according to the conventional method and compressed into tablets containing 50 mg of the main drug.

Preparation example 2

Active ingredient	50 mg
Lactose	90 mg
Corn starch	60 mg

8

Talc	30 mg
Magnesium stearate	10 mg

The above compounds were granulated according to the conventional method to make granules.

Preparation example 3

Active ingredient	10 mg
Solubilizer (used as desired)	a suitable amount
Sodium chloride (used as desired)	a suitable amount
Distilled water for injection	1 ml

The above compounds were admixed according to the conventional method and then filled into ampoules to make ampoules for injection.

Pharmacological study

(1) Platelet aggregation inhibitory action

Platelet aggregation inhibitory action of the compounds of the present invention was measured according to the method described by Born (G.V. Born, Nature, 927-929, (1962)). Thus, citric acid-added blood was drawn from Japanese white male rabbits, which was then centrifuged to obtain platelet-rich plasma (PRP) and platelet-poor plasma (PPP). 1.5 µl of test compounds dissolved in dimethyl sulfoxide (DMSO) was added to 270 µl of PRP. After incubating at 37 °C for 1 minute, arachidonic acid (AA) was added to induce aggregation. Platelet aggregation was measured by NKK Hematracer, and 50% inhitibory concentrations (IC_{50} µM) of the test compounds were obtained from the concentration-inhibition ratio curve. Aspirin was used as a control drug. The results of the representative examples are shown in Table 2.

Table 2

Test cmpds. Example No.	Arachidonic acid IC50 μM	Test cmpds. Example No.	Arachidonic acid IC50 μM
1	5.5	12	5.3
2	1.8	13	0.5
3	1.9	15	5.6
4	14.4	16	4.6
5	1.7	17	10.6
6	5.6	18	5.7
7	12.8	19	5.9
8	17.0	22	1.8
9	1.7	24	0.5
10	1.6		
11	2.6	Aspirin	172.0

(2) Effects on an arachidonic acid (AA)-induced pulmonary thrombosis death model

This study was performed according to the method described by Silver et al. (Science, 183, 1085 (1974)). Thus, Japanese white male rabbits after 24-hour fasting were administered AA (1.6 mg/kg) dissolved in 0.1 M sodium carbonate in the veins of the ear to induce pulmonary thrombosis death due to platelet aggregation. The test compounds at a dose of 100 mg/kg were orally given one hour before AA administration. The effects were assessed by the death rate at 5 hour after AA administration. The results are shown in Table 3.

Table 3

Example No.	No. of death/Total number
1	0/2
Control group	3/3

(3) Effects on an arachidonic acid (AA)-induced thrombocytopenia model

This study was performed according to the method described by Griffett et al. (Griffett et al. Br. J. Pharmacol., 72, 697, (1981)). Thus, ddy male mice after 16-hour fasting were administered AA (15 mg/kg) dissolved in 0.1 M sodium carbonate in the tail veins. Fifteen seconds later, 0.1 ml of blood was drawn by cardiocentesis under unanesthesia into a syringe containing 10 µl of 10% EDTA•2Na to determine platelet counts using an automatic platelet counter (Toa Iyo Denshi, PL-110). The test compounds at a dose of 100 mg/kg were orally given 1 hour before AA administration. The effects were assessed with the activity of aspirin (300 mg/kg, p.o.) as 100%. The results are shown in Table 4.

Table 4

Example No.	Activity
1	243.4
5	205.4
6	300.0
8	162.9
Aspirin	100

Toxicity study

(1) Acute toxicity study on mice

The test compounds of examples 1, 5, 6, and 8 were suspended in an aquous solution of 0.5% carboxy methyl cellulose and were given orally to ddy male mice (5 mice per group). The conditions of the animals were observed for 7 days after administration. As a result, no death was observed at a dose of 1000 mg/kg of any of the above compounds.

Effects of the invention

The compounds of the present invention show an extremely low toxicity in the toxicity study using mice. In the pharmacological actions, they show excellent activities more potent than aspirin in in vitro platelet aggregation inhibitory action and excellent actions as anti-thrombotic agents in prevention and treatment of, for example, cerebral thrombosis, cerebral infarction, peripheral arteriostenosis and the like.